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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ROCHE MOLECULAR SYSTEMS INC
PATENT LAW DEPARTMENT
1145 ATLANTIC AVENUE
ALAMEDA, CA 94501

EXAMINER

STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 12/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/530,746

Applicant(s)

KESSLER ET AL.

Examiner

Teresa E Strzelecka

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 August 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ * Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 14082003. 6) ☐ Other: _____

DETAILED ACTION

1. This office action is in response to an amendment filed on August 14, 2003. Claims 1-25 were previously pending. Applicants cancelled claims 16-25 and amended claims 1, 3, 4 and 6-9. Applicants' amendments and arguments overcame the following rejections: rejection of claims 1-15 under 35 U.S.C. 112, second paragraph; rejection of claims 1-3, 5-7, 10 and 14 under 35 U.S.C. 102(b) over Whitby et al.; rejection of claim 8 under 35 U.S.C. 103(a) over Whitby et al. and Livak et al.; rejection of claim 9 under 35 U.S.C. 103(a) over Whitby et al. and Wittwer; rejection of claim 15 under 35 U.S.C. 103(a) over Whitby et al. and Koster.
2. Claims 1-15 are pending and will be examined. This office action is made non-final because of new grounds for rejection.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on August 14, 2003 was filed after the mailing date of the first office action on March 26, 2003. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
5. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is indefinite because it is not clear whether the detection by mass spectroscopy is achieved with the probe bound to the detected amplificate, or whether only the amplificate is detected, in which case there is a missing step of dissociating the probe from the amplificate.

Claim interpretation

6. The terms “non-specific primer” or “non-specific probe” are interpreted as primers and probes which are used to amplify and detect several different targets simultaneously.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3, 5-7, 10 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Birkenmeyer et al. (U.S. Patent No. 5,453,355).

Regarding claim 1, Birkenmeyer et al. teach a method for the detection of a nucleic acid comprising the steps:

(a)- producing a plurality of amplificates of a section of the nucleic acid with the aid of two primers, one of which binds to a binding sequence A', which is complementary to a sequence A of one strand of the nucleic acid and the other binds to a binding sequence which is located in the 3' direction from A and does not overlap A (Birkenmeyer et al. teach amplification of *Neisseria gonorrhoeae* by polymerase chain reaction (= producing a plurality of amplificates), using primers pairs in which one of the primers binds to a sequence on a (+) strand of the *N. gonorrhoeae* sequence fragment extending from bp 827-972, and a second primer which

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binds to a sequence 3' from the first primer and is complementary to the (-) strand (Fig. 1; Table 1).),

(b)- contacting the amplicates with a probe having a binding sequence D which binds either to a sequence B or to the complement thereof, wherein the sequence B is located between the sequences A and C (Birkenmeyer et al. teach contacting the amplified fragments with a probe having a binding sequence on the (+) strand and located between the primer sequences (Table 1; col. 6, lines 31-43).), and

(c)- detecting the formation of a hybrid of the amplicate and probe (Birkenmeyer et al. teach detection of the complex between the amplicate and the probe by gel electrophoresis (col. 9, lines 12-34; Fig. 2),

wherein the sequence located between the sequences A and C contains no nucleotides or less than 3 nucleotides that do not belong to the sequence region E formed from the binding sequence D of the probe and the sequence of the amplicate bound thereto and the amplicates are shorter than 100 nucleotides (Birkenmeyer et al. teach a probe with SEQ ID NO: 8, which spans bp 894-936 of the *N. gonorrhoeae* pil E gene (Table 1). The primer pairs 5 (SEQ ID NO: 4 and 5) and 6 (SEQ ID NO: 4 and 7) amplify DNA fragments of 57 and 51 bp, respectively, with the probe spanning the whole first primer and extending 2 bp into the second primer. Similarly, primer pairs 8 (SEQ ID NO: 6 and 5) and 9 (SEQ ID NO: 6 and 7) amplify DNA fragments of 50 and 44 bp, respectively, with the probe spanning the whole first primer and extending 2 bp into the second primer. Therefore Birkenmeyer et al. teach the limitation of no nucleotides between primer sequences which do not belong to the complex between the amplicate and the probe and the limitation of an amplicate shorter than 100 bp; see Fig. 2).

Regarding claim 2, Birkenmeyer et al. teach the probe overlapping with primer sequences of primers with SEQ ID NO: 4, 5, 6 and 7 (Table 1; see explanation for claim 1).

Regarding claim 3, Birkenmeyer et al. teach a primer in which the 5' end (=non-extendible part) contains nucleotides which are not complementary to the target sequence, therefore they do not hybridize to the target sequence (col. 5, lines 45-48).

Regarding claim 5, Birkenmeyer et al. teach amplicates which are 57, 51, 50 or 44 bp in length (Table 1; Fig. 2), therefore do not exceed 74 bp.

Regarding claims 6 and 7, Birkenmeyer et al. teach primers which are immobilizably-labeled with a hapten, which is then used to capture the amplicate (col. 7, lines 25-40), detectably-labeled probe (col. 6, lines 39-45) and detectably-labeled primers (col. 7, lines 19-21). Birkenmeyer et al. teach that the probe may be immobilized and the hapten detected or vice versa (col. 7, lines 44-48).

Regarding claim 10, Birkenmeyer et al. teach detection of the amplicate by gel electrophoresis (= physical means) and autoradiography (= spectroscopic method) (col. 9, lines 12-34).

Regarding claim 14, Birkenmeyer et al. teach nucleotides complementary to A, G, C and T in the amplification reaction (col. 8, lines 63-65).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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10. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Birkenmeyer et al. and Livak et al. (U. S. Patent No. 5,538,848; cited in the IDS and in the previous office action).

A) Claim 8 is drawn to a probe labeled with a fluorescence quencher and a fluorescent dye.

B) Teachings of Birkenmeyer et al. are described above. Birkenmeyer et al. teach labeled probes, but do not teach a probe labeled with a fluorescence quencher and a fluorescent dye.

C) Livak et al. teach a probe labeled with a reporter molecule (= fluorescent dye) and a quencher, the probe being used for monitoring of the progress of amplification reaction (Abstract; Figure 1; col. 3, lines 29-56; col. 5, lines 38-58).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the reporter-quencher labeled probe of Livak et al. in the detection method of Birkenmeyer et al. The motivation to do so, provided by Livak et al., would have been that real-time quantitation of nucleic acid amplification was achieved using such probe, and real-time monitoring of amplification prevented cross-contamination of samples, especially important in diagnostic applications (col. 1, lines 22-52; col. 3, lines 8-12).

11. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Birkenmeyer et al. and Wittwer (U. S. Patent No. 6,245,514 B1; cited in the previous office action).

A) Claim 9 is drawn to one of the primers labeled with a first energy transfer component and a probe labeled with a second energy transfer component which is different from the first energy transfer component.

B) Teachings of Birkenmeyer et al. are described above. Birkenmeyer et al. teach labeled primers and probes, but do not teach one of the primers labeled with a first energy transfer component and a probe labeled with a second energy transfer component which is different from the first energy transfer component.

C) Wittwer teaches fluorescence energy transfer pairs for detecting the presence of target analyte. Wittwer teaches detection of PCR products by resonance energy transfer between one labeled primer and one labeled probe which hybridizes between the PCR primers. Exemplary energy transfer pair can comprise fluorescein as a donor and Cy5 or Cy5.5 as the acceptor (col. 3, lines 66, 67; col. 4, lines 1-3; col. 5, lines 63-67; col. 6, lines 1-13, 54, 55; col. 7, lines 31-52; col. 31, lines 35-67; col. 32, lines 1-63).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the donor-acceptor energy transfer between a primer and a probe of Wittwer in the detection method of Birkenmeyer et al. The motivation to do so, provided by Wittwer, would have been that using labeled probe and primer provided "a superior monitor of product accumulation for quantitation" and resulted in more precise measurement of fluorescence intensity than other methods (col. 32, lines 6-18 and 59-63).

12. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Birkenmeyer et al. and Koster (WO 96/29431, cited in the IDS and in the previous office action).

A) Claim 15 is drawn to the detection of amplicates by mass spectroscopy.

B) Teachings of Birkenmeyer et al. are described above. Birkenmeyer et al. do not teach detection of amplicates by mass spectroscopy.

C) Koster teaches detection of nucleic acids by mass spectrometry. Koster teaches detection of an amplified target nucleic acid (= amplicate) by immobilization of the target nucleic acid on a solid support and detection of the target by mass spectrometry. Immobilization of the target can be achieved by hybridizing the target with a capture probe which has been immobilized on solid support (page 4, lines 15-38; page 5, lines 1-11; Figure 1A; Figure 4; page 15, lines 34-39; page 16,

lines 1-28). Mass spectrometry was used to detect a 67 bp amplification product from hepatitis B virus (HBV) (page 27, lines 24-39; page 28-30).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used mass spectrometry detection of PCR products of Koster in the detection method of Birkenmeyer et al. The motivation to do so, provided by Koster, would have been that mass spectrometry provided high detection sensitivity and accuracy of mass, i.e., molecular weight, determination (page 2, lines 33-37).

13. Claims 4 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Birkenmeyer et al. and Greisen et al. (J. Clin. Microbiol., vol. 32, pp. 335-351, 1994).

A) Teachings of Birkenmeyer et al. are described above. Birkenmeyer et al. do not teach amplification of a nucleic acid target with primers or probes which are not specific for the nucleic acid.

B) Greisen et al. teach amplification of bacteria causing meningitis using universal (= non-specific) primers and probes, with which a number of bacterial species found in CSF were amplified and detected. The primers were DG74, RW01 and RDR080 (Table 3). These primers amplified 18 species of bacteria found in CSF (page 343, first paragraph; Table 1). In addition, universal probes for different bacterial species were designed, with probe COR28 designed to detect *N. meningitis* serotypes and *N. gonorrhoeae* (page 343, sixth paragraph; Table 4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the non-specific primers and probes of Greisen et al. in the method of Birkenmeyer et al. The motivation to do so, provided by Greisen et al., would have been that amplification with non-specific primers and detection with non-specific probes provided a very sensitive way of detecting pathogenic bacteria in CSF, as 10 copies of *E. coli* DNA, corresponding

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to three E. coli cells, were detected (page 349, fourth paragraph). As stated by Greisen et al., "... A clinical PCR assay based on these primers may have sufficient sensitivity to allow direct detection of bacteria in CSF without an intermediate culturing step..." (page 349, fourth paragraph), and "...The PCR primers and panel of probes described here can form the basis of a more rapid and sensitive means of detecting bacteria in clinical samples." (page 350, last paragraph).

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1, 4, 5, 8 and 11-14 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3-9 of copending Application No. 09/530,747.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claims. See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

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Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 is generic to all that is recited in claim 1 of the 09/530,747 application. That is, claim 1 of the 09/530,747 application falls entirely within the scope of claim 1 of the instant application, or, in other words, claim 1 is anticipated by claim 1 of the 09/530,747 application. Specifically, claim 1 of the instant application is drawn to a method of detection of nucleic acids comprising the steps:

- (a)- producing a plurality of amplicates of a section of the nucleic acid with the aid of two primers, one of which binds to a binding sequence A', which is complementary to a sequence A of one strand of the nucleic acid and the other binds to a binding sequence which is located in the 3' direction from A and does not overlap A,
- (b)- contacting the amplicates with a probe having a binding sequence D which binds either to a sequence B or to the complement thereof, wherein the sequence B is located between the sequences A and C, and
- (c)- detecting the formation of a hybrid of the amplicate and probe,

wherein the sequence located between the sequences A and C contains no nucleotides or less than 3 nucleotides that do not belong to the sequence region E formed from the binding sequence D of the probe and the sequence of the amplicate bound thereto and the amplicates are shorter than 100 nucleotides.

Claim 1 of the 09/530,747 application is drawn to the method in which the probe has a reporter group and a quencher group, the polymerase has a 5' nuclease activity and the amplicates have fewer than 75 nucleotides, which makes this claim a species of a genus defined by claim 1 of the instant application. The dependent claims 3-9 of the 09/530,747 application are identical to claims 4, 5, 8, and 11-14 of the instant application, therefore they anticipate these dependent claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of copending Application No. 09/530,929.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claims. See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 is generic to all that is recited in claim 1 of the 09/530,929 application. That is, claim 1 of the 09/530,929 application falls entirely within the scope of claim 1 of the instant application, or, in other words, claim 1 is anticipated by claim 1 of the 09/530,929 application. Specifically, claim 1 of the instant application is drawn to a method of detection of nucleic acids comprising the steps:

(a)- producing a plurality of amplicates of a section of the nucleic acid with the aid of two primers, one of which binds to a binding sequence A', which is complementary to a sequence A of one strand of the nucleic acid and the other binds to a binding sequence which is located in the 3' direction from A and does not overlap A,

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(b)- contacting the amplicates with a probe having a binding sequence D which binds either to a sequence B or to the complement thereof, wherein the sequence B is located between the sequences A and C, and

(c)- detecting the formation of a hybrid of the amplicate and probe,

wherein the sequence located between the sequences A and C contains no nucleotides or less than 3 nucleotides that do not belong to the sequence region E formed from the binding sequence D of the probe and the sequence of the amplicate bound thereto and the amplicates are shorter than 100 nucleotides.

Claim 1 of the 09/530,929 application is drawn to the method in which the sequence between the binding sequences A and C contains no nucleotides that do not belong to the sequence region E of the amplicate that is bound by binding sequence D of the probe, which makes this claim a species of a genus defined by claim 1 of the instant application. The dependent claims 2-15 of the 09/530,929 application are identical to claims 2-15 of the instant application, therefore they anticipate these dependent claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).


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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

The examiner will move to the new office in Alexandria on January 8, 2004. The new phone number in that office is (571) 272-0789. Gary Benzion will move to the new office on January 22, 2004. His new phone number is (571) 272-0782.

TS
December 10, 2003



JEFFREY FREDMAN
PRIMARY EXAMINER